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Editorial
Plasminogen Receptors

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Plasminogen is the circulating zymogen of the broad spectrum serine protease, plasmin, the enzyme responsible for thrombus dissolution. In the mid 1980's it was first recognized that plasminogen also interacts with the surfaces of cells. This interaction is functionally important because the plasminogen activators, urokinase, and tissue plasminogen activator have, by themselves, a very limited capability to activate plasminogen. However, once the plasminogen activators bind to cellular receptors their ability to activate plasminogen is increased dramatically. The plasmin that is produced remains associated with the cell surface and is protected from inactivation by the plasmin inhibitor, α_2-antiplasmin. This results in localization of the broad proteolytic activity of plasmin on cell surfaces, promoting the ability of cells to degrade extracellular matrices and activate other matrix-associated proteolytic enzymes and growth factors that facilitate cell migration. Thus, the interaction of plasminogen with cells plays a major role in macrophage recruitment during the inflammatory response, tumor cell invasion and metastasis, wound healing, tissue remodeling, neurite outgrowth, and skeletal myogenesis. Additional key functions of cell-associated plasmin are promotion of prohormone processing and induction of intracellular signaling pathways. Plasminogen-binding sites are broadly distributed on both eukaryotic and prokaryotic cell types, and the majority of cells have a very high capacity for binding plasminogen. Thus, no single molecule can account for the entire plasminogen-binding capacity of a given cell type. Notably, a subset of plasminogen-binding sites that expose a C-terminal basic residue on the cell surface are predominantly responsible for the ability of eukaryotic cells to promote plasminogen activation. Over the past two and a half decades specific plasminogen-binding proteins that promote plasminogen activation on both prokaryotic and eukaryotic cells have been identified. Recent studies using overexpression, specific knockdown, specific antibody blockade, proteomics approaches, and transgenic mice have identified new functions for plasminogen receptors. The papers selected for this issue are representative of state-of-the-art studies in plasminogen receptor biology in 2012.

This special issue contains seventeen papers, where thirteen address plasminogen receptors on eukaryotic cells and four address plasminogen receptors on prokaryotic cells.

Within the eukaryotic category, six papers address key functional consequences of the interaction of plasminogen with the entire complement of plasminogen receptors on a given cell surface and address mechanisms of these interactions.

In "*Cell surface remodeling by plasmin: a new function for an old enzyme,*" E. Deryugina and J. Quigley present the evidence linking *de novo* generated activity of plasmin and its catalytic manifestations in oncogenesis. For example, this group has shown that cell-associated plasmin catalyzes the cleavage, *in vivo,* of the CUB domain-containing protein 1 (CDCP1), a transmembrane protein overexpressed in many cancers and thought to regulate cell resistance to anoikis.

Plasmin-mediated cleavage of CDCP1 leads to outside-in signaling involving activation of Akt and suppression of PARP1-induced apoptosis *in vivo*. This signaling cascade ultimately regulates the survival potential of tumor cells in the late stages of the metastatic cascade, namely, during extravasation and early tissue colonization. The results also suggest that the original link of the uPA-plasmin system with cancer may not all be via protease-mediated invasive migration, but rather via plasmin cleavage of cell survival signaling molecules.

In "*The serine protease plasmin triggers expression of the CC-chemokine ligand 20 in dendritic cells via Akt/NF-kappaB-dependent pathways,*" X. Li et al. demonstrate that plasmin triggers release of the chemokine CCL20 via activation of Akt and MAP kinase followed by activation of NF-κB. This may facilitate accumulation of $CCR6^+$ immune cells in areas of plasmin generation such as inflamed tissues including atherosclerotic tissues.

In "*The plasminogen system in regulating stem cell mobilization,*" Y. Gong and J. Hoover-Plow present the potential mechanisms by which the plasminogen system regulates stem cell mobilization, focusing on step-wise proteolysis and signal transduction during the egress of hematopoietic progenitor and stem cells (HPSCs) from their bone marrow niche. Clear elucidation of the underlying mechanisms may lead to the development of new plasminogen-based therapeutic strategies to improve stem cell mobilization in treating hematological and cardiovascular diseases.

In "*Characterization of plasminogen binding to NB4 promyelocytic cells using monoclonal antibodies against receptor-induced binding sites in cell-bound plasminogen,*" M. Jardí et al. demonstrate that NB4 cells, which display many of the characteristics of acute promyelocytic leukemia blast cells, exhibit reduced binding of plasminogen when treated with all-*trans* retinoic acid, as detected with a monoclonal antibody that specifically reacts with cell-associated, compared with soluble plasminogen. This cell line constitutes an unique model to explore plasminogen binding and activation that can be modulated by all-*trans* retinoic acid treatment.

In "*Ocriplasmin for vitreoretinal diseases,*" I. Tsui et al. discuss a series of clinical trials to study ocriplasmin (Microplasmin, ThromboGenics, Iselin, NJ), a novel ophthalmic medication, for the treatment of vitreoretinal diseases such as vitreomacular traction, macular hole, and exudative age-related macular degeneration. The results are promising and may impact patient care.

In "*Accelerated fibrinolysis and its propagation on vascular endothelial cells by secreted and retained tPA,*" T. Urano and Y. Suzuki discuss successful visualization of the secretory dynamics of tissue-type plasminogen activator (tPA) tagged by green fluorescent protein (tPA-GFP) from cultured vascular endothelial cells (VECs) using total internal reflection fluorescence (TIRF) microscopy and demonstrate that tPA-GFP secreted from VECs is retained on cell surfaces in a heavy-chain-dependent manner. Progressive binding of Alexa568-labeled Glu-plasminogen was also observed on the surface of active tPA-GFP-expressing cells, which was not observed on cells expressing an inactive active site mutant tPA-GFP. These results suggest that retained tPA on VECs effectively activated plasminogen to plasmin, which then facilitated the binding of additional plasminogen on the cell surface by proteolytically cleaving surface-associated proteins and exposing their C-terminal lysyl residues.

Also within the eukaryotic cell category, seven papers address the functions of specific plasminogen receptors.

In "*Alpha-enolase, a multifunctional protein: its role in pathophysiological situations,*" A. Diaz-Ramos et al. review the multiple roles of α-enolase as a plasminogen receptor and its role in several pathologies. For example, this group has shown that α-enolase is expressed on the surfaces of differentiating myocytes and that inhibitors of plasminogen binding to α-enolase block myogenic fusion *in vitro* and skeletal regeneration in mice.

In "*The biochemistry and regulation of S100A10: a multifunctional plasminogen receptor involved in oncogenesis,*" P. Madureira et al. present the structure, function, and regulation of the plasminogen receptor S100A10. The S100A10-null mouse model has established the critical role that S100A10 plays as a regulator of fibrinolysis and two of its roles in oncogenesis, firstly as a regulator of cancer cell invasion and metastasis and secondly as a regulator of the recruitment of tumor-associated cells, such as macrophages, to the tumor site.

In "*The Annexin A2/S100A10 system in health and disease: emerging paradigms,*" N. Hedhli et al. review evidence that the annexin A2/S100A10 heterotetramer is dynamically regulated in settings of hemostasis and thrombosis and that this complex functions in regulating generation of plasmin. The manipulation of the annexin A2/S100A10 system may offer promising new avenues for treatment of a spectrum of human disorders.

In "*Potential role of kringle-integrin interaction in plasmin and uPA actions (a hypothesis),*" Y. Takada proposes a model in which upon plasminogen activation, an integrin-binding site in plasmin is exposed and, once activated, plasmin is able to bind to integrins on the cell surface through the kringle domains (since integrin-binding sites are exposed) and proteolytically activates PAR-1, which induces intracellular signaling.

In "*The plasminogen receptor, Plg-R_{KT}, and macrophage function,*" L. Miles et al. describe the use of proteomics to identify a plasminogen receptor with a unique structure, the novel transmembrane protein, Plg-R_{KT}, which is synthesized with and exposes a C-terminal lysine on the cell surface. Plg-R_{KT} promotes plasminogen activation, cell migration, and macrophage recruitment in the inflammatory response.

In "*The plasminogen activation system and the regulation of catecholaminergic function,*" H. Bai et al. present a mechanism by which neurotransmitter release from catecholaminergic cells is negatively regulated by cleavage products formed from plasmin-mediated proteolysis. Plg-R_{KT} is highly expressed in chromaffin cells of the adrenal medulla as well as other catecholaminergic cells and tissues, and Plg-R_{KT}-dependent plasminogen activation plays a key role in regulating catecholaminergic neurosecretory function.

In "*So many plasminogen receptors: why?*" E. Plow et al. discuss potential reasons for the expression of different plasminogen receptors. Different plasminogen receptors may be

utilized to achieve specific steps in plasminogen-dependent physiologic and pathologic functions.

The four papers addressing prokaryotic plasminogen receptors are summarized below.

In "*Bacterial plasminogen receptors utilize host plasminogen system for effective invasion and dissemination,*" S. Bhattacharya et al. review mechanisms by which pathogenic bacteria engage plasminogen, which is activated to plasmin to trigger development of a proteolytic surface on the bacteria. Bacteria, thus, exploit the host plasminogen and fibrinolytic system for the successful dissemination within the host.

In "*Plasminogen binding proteins and plasmin generation on the surface of Leptospira spp.—the contribution to the bacteria-host interactions,*" M. Vieira et al. review the ability of several species of pathogenic *Leptospira* to bind human plasminogen and to generate enzymatically active plasmin on the bacteria surface and the identification and characterization of several proteins that may act as plasminogen receptors. The presence of plasmin on the leptospiral surface may facilitate host tissue penetration and help the bacteria to evade the immune system and, as a consequence, permit *Leptospira* to reach secondary sites of infection.

In "*The role of nephritis-associated plasmin receptor (NAPlr) in glomerulonephritis associated with streptococcal infection,*" T. Oda et al. review the isolation of a nephritogenic antigen for acute poststreptococcal glomerulonephritis, highly identical to the reported plasmin(ogen) receptor of Group A Streptococcus. Deposition of this nephritogenic antigen may contribute to the pathogenesis of acute poststreptococcal glomerulonephritis by maintaining plasmin activity.

In "*Bacterial plasminogen receptors: mediators of a multifaceted relationship,*" M. Sanderson-Smith et al. provide an overview of bacterial plasminogen receptors and discuss the diverse roles bacterial plasminogen acquisition plays in the relationship between bacteria and host. Numerous bacterial plasminogen receptors have been identified, and the mechanisms by which they interact with plasminogen are diverse.

Thus, the papers in this special issue, representing a broad spectrum of experimental approaches and areas of investigation, demonstrate the wide array of cellular events and functions that are mediated by the interaction of plasminogen with cellular receptors. This unique and informative collection of papers on plasminogen receptors summarizes the research of the past 25 years and highlights the direction of future studies. This special issue, therefore, showcases the fundamentally important role that plasminogen receptors play in physiological and pathophysiological processes.

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